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A validated prediction model for end-stage kidney disease in type 1 diabetes

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Short title: Predicting end-stage kidney disease in type 1 diabetes

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Research in context

Evidence before this study

End-stage kidney disease is a life-threatening complication of type 1 diabetes. Although, the incidence of end-stage kidney disease has decreased over the last decades, the decline is substantially lower in comparison with other common diabetes-related complications such as cardiovascular disease. Fortunately, end-stage kidney disease can be prevented or delayed by intervention, and early detection of persons at increased risk is essential. We searched PubMed for research articles published up to September 30, 2020 and selected key evidence. There are currently no risk prediction models developed specifically for end-stage kidney disease in type 1 diabetes.

Added value of this study

We have derived and validated a novel, high-performing prediction model for assessing risk of end-stage kidney disease in adults with type 1 diabetes. The model includes information that are routinely collected from clinical examinations.

Implications of all the available evidence

The prediction model showed excellent performance both internally and externally, indicating high usability in clinical practice. This model may improve clinical decision making and potentially guide early intervention.

Abstract

Background End-stage kidney disease (ESKD) is a life-threatening complication of type 1 diabetes (T1D) which can be prevented or delayed by intervention. Hence, early detection of persons at increased risk is essential.

Methods From a population-based cohort of 5,460 clinically diagnosed Danish adults with T1D followed 2001-2016, we developed a prediction model for ESKD accounting for the competing risk of death. Poisson regression analysis was used to estimate the model based on information routinely collected from clinical examinations. The effect of including an extended set of predictors (lipids, alcohol intake etc.) was further evaluated, and potential interactions identified in a survival tree analysis were tested. The final model was externally validated in 9,175 T1D adults from Denmark and Scotland.

Findings During a median follow-up of 10·4 years (interquartile limits: 5·1;14·7), 303 (5·5%) of the participants (mean (SD) age 42·3 (16·5) years) developed ESKD and 764 (14·0%) died without having developed ESKD. The final ESKD prediction model included age, male sex, diabetes duration, estimated glomerular filtration rate, micro- and macroalbuminuria, systolic blood pressure, HbA_{1c}, smoking and previous cardiovascular disease. Discrimination was excellent for 5-year risk of ESKD event with a C-statistic of 0·888 (95%CI: 0·849;0·927) in the derivation cohort and confirmed at 0·865 (0·811;0·919) and 0·961 (0·940;0·981) in the external validation cohorts from Denmark and Scotland.

Interpretation We have derived and validated a novel, high-performing ESKD prediction model for risk stratification in the adult T1D population. This model may improve clinical decision making and potentially guide early intervention.

Funding None

Introduction

The observed incidence of end-stage kidney disease (ESKD) in persons with type 1 diabetes (T1D) has stabilised¹ or decreased over the last decades,²⁻⁴ probably related to the increased use of renin-angiotensin system (RAS) blockers. However, the decline in ESKD risk has been substantially lower in comparison with other common diabetes-related complications such as cardiovascular disease,^{1,5} and ESKD still remains a life-threatening complication⁶ with a 10-fold increase in mortality rate in T1D.³

Fortunately, ESKD can be prevented or delayed by intensive glucose- and blood pressure lowering therapy,⁷ and early detection is therefore essential. ESKD often develops in persons with complicated and poorly controlled T1D.⁶ This group also face a high degree of pre-ESKD death, especially in the older ages.³ Because death precludes the occurrence of ESKD, a person's risk of developing ESKD also depends on overall mortality risk. Not considering the "competing" risk of death is likely to overestimate the absolute risk of ESKD.^{8,9} Because the decision to initiate ESKD preventive treatment is often based on the absolute risk of developing ESKD, it is essential to estimate individual ESKD risk accurately.

Prediction models for ESKD in diabetes are scarce. Except for one study using a composite outcome of end-stage renal failure, coronary heart disease, stroke, amputations, blindness and death,¹⁰ and one study predicting renal function decline,² there is, to our knowledge, no ESKD risk models developed for the T1D population. Three prediction models have been developed for cohorts of people with T2D, one in New Zealand¹¹ and two in Chinese adults.^{12,13} T1D differs from T2D, in that persons with T1D are generally diagnosed at younger ages and therefore exposed to diabetes-related risk factors for ESKD, such as hyperglycaemia and hypertension, for a longer time. Furthermore, while increased blood pressure, chronic kidney

disease and smoking appear to be risk factors for ESKD in both types of diabetes, obesity seems to play a larger role in T2D,¹⁴ whereas age at diabetes diagnosis is mainly a risk factor in T1D.^{3,14,15} This suggests a difference in the pathophysiology of ESKD for T1D and T2D, and prediction models specific to the T1D population are needed.

Change in eGFR is a predictor of ESKD in diabetes,² and the KDOQI Clinical Practice Guidelines for diabetes and CKD suggest monitoring the rate of decline in eGFR to predict the time to onset of kidney failure.¹⁶ However, information on prior eGFR trajectory in persons with T1D requires continuous monitoring of eGFR which is not widely feasible. Hence, the ability to assess ESKD risk in T1D based on current levels of risk factors is needed.

The aim of this study was to develop a risk prediction model for ESKD accounting for the competing risk of death, using a large population-representative cohort of adults with T1D with an extensive range of clinical data and information on ESKD events and mortality from national registers. We externally validated the model in national and international cohorts to assess its broader generalisability.

Methods

Study design and data sources

The study is based on a large population-based cohort of 5,506 adults T1D treated at the outpatient clinic at Steno Diabetes Center Copenhagen (SDCC) in the period from January 1st, 2001 to December 31st, 2016. In Denmark, treatment of persons with T1D is based in tertiary care and referral to specialist care is free of charge. The T1D population at SDCC includes the entire adult age span with both newly diagnosed and long-term diabetes, reflecting the background population with T1D within this region. Individuals were followed from the date

of their first clinical examination with a measurement of serum creatinine until first event of ESKD, death, emigration, or until censor date December 31st, 2016 (date of register extraction).

To ensure exclusion of extreme values of metabolic risk factors such as haemoglobin A1c (HbA_{1c}) and lipids often present at the time of diagnosis, clinical examinations within the first year of diabetes diagnosis were excluded from the analyses. We further excluded persons with prevalent ESKD at their first clinical examination ($n = 46$ (0.8%)), leaving 5,460 persons with T1D with a total of 42,921 clinical examinations for analysis.

According to Danish law, ethics approval and participant consent is not required for registry-based studies. Access and use of the described data were approved by the Danish Data Protection Agency (j-No: VD-2019-197) and the Danish Patient Safety Authority (j-No: 3-3013-2959/1).

Outcome and exposures

Detailed clinical data of the participants were collected from the electronic health records at SDCC and linked to nationwide registries on mortality and morbidity including ESKD,^{17,18} using the unique personal identification number given to all Danish residents at birth or at immigration.¹⁹

Clinical data from the electronic health records

To separate diabetes type 1 from type 2, T1D was clinically diagnosed based on phenotype and in accordance with the Danish National Diabetes Quality Database requirements.

Electronic health data on all clinical visits with a measurement of serum creatinine were extracted together with the corresponding clinical- and behavioural data. Detailed information on how measurements were obtained have been reported previously^{20,21}.

Albuminuria was classified from 24-hour sterile urine collections (mg/24h) or spot urine (mg/g) into normoalbuminuria (<30), microalbuminuria (30-299) or macroalbuminuria (\geq 300). We categorised smoking status into current smoking (yes/no), physical activity into regular physical activity defined as \geq 30 minutes per day (yes/no), alcohol intake in three classes (0, 1–20, and >20 units/week), use of antihypertensive treatment (yes/no), lipid-lowering treatment (yes/no), and RAS blocking treatment (yes/no). Retinopathy status was assessed from retinal photographs (no retinopathy, mild/moderate retinopathy or severe retinopathy). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation. (see supplemental material for further details).

Data from national registries

Previous CVD was defined as any previous event of ischemic heart disease, ischemic stroke, heart failure, and peripheral artery disease as previously defined.²¹ We defined ESKD as a composite event of CKD stage 5 (ICD-10 code DN185), dialysis (procedure code BJFD), kidney transplantation (procedure code KKAS) or an eGFR <15 mL/min/1.73m². ESKD event data was obtained from the Danish National Patient Register.¹⁸ Data on date and cause of death was collected from the Cause of Death Register.¹⁷ Death without having developed ESKD was defined as non-ESKD related mortality. Data on ethnicity were obtained from the Central Person Register¹⁹ and ethnicity in the present study was defined as geographical region of

origin (European, Middle East or Other). The registers are nationwide and cover all Danish residents.

Statistical analysis

To account for the competing risk of death, cause-specific rate models for ESKD and death were estimated and then combined into a model for cumulative ESKD risk using the conditional survival function.⁸

We first developed a *core model* from commonly measured factors including age, sex, diabetes duration, eGFR, albuminuria status, systolic- and diastolic blood pressure, HbA_{1c}, smoking and previous CVD, and an *extended model* which further included RAS blocking treatment, other antihypertensive treatment, lipid-lowering treatment, BMI, ethnicity, retinopathy, total- and HDL cholesterol, LDL cholesterol, triglycerides, haemoglobin, alcohol intake, regular exercise, height, urinary albumin-to-creatinine ratio (UACR), potassium, sodium, TSH. Predefined interactions between clinical measurements and treatment, as well as other interactions between predictors identified in a prior conditional survival trees analysis were included in both models.

In a subset of 4,815 (88%) participants with at least two clinical examinations, we further tested the effect of including eGFR annual change prior to baseline in the *core model*.

The cause-specific rate models for ESKD and death were estimated separately using Poisson models with log of the risk time as offset and censoring for the other event. For each participant, the follow-up period was split into 1-year age bands and further at the time points of repeated clinical examinations during follow-up. At each time interval, the most recent values of the

predictors were used, and age and diabetes duration were updated. Before analysis, predictors with a highly skewed distribution were log2-transformed to improve model calibration. Backwards elimination was used to test the predictors and interactions. The level of statistical significance was set at 5%.

Post-estimation shrinkage factors for the predictors were estimated in all the cause-specific rate models.²²

The discriminatory power of the models was evaluated using the C-statistic²³ with confidence interval computed from the DeLong method. In addition, model calibration was determined with Hosmer-Lemeshow test of goodness of fit²⁴ by comparing means of estimated cumulative ESKD risk with the corresponding observed incidence in deciles of estimated risk.

Multivariate imputations by chained equations was used to impute missing values and estimates summarised according to Rubin's rules. Details of the statistical analysis are supplied in the supplemental material.

Validation

The cumulative incidence functions for ESKD with the original regression coefficients in both the *core*- and *extended models* were internally validated using the first clinical examination of the derivation cohort.

The cumulative incidence function for ESKD with both the original and the shrunken regression coefficients for the *core model* was externally validated nationally in the T1D population of the Danish Funen Diabetes Database (FDDB)²⁵ and internationally in the Scottish

Diabetes Research Network Type 1 Bioresource (SDRNT1BIO)². The validation cohorts did not have the required data available for validation of the *extended model*.

In FDDb, where we had access to baseline eGFR, discrimination and model calibrations for a 5-year and 10-year ESKD event among participants with $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$ at baseline was also calculated. This subgroup constituted 91% of the FDDb study participants but accounted for only 41% and 46% of the ESKD events after 5- and 10 years of follow-up.

Statistical analyses were performed in R version 3.6.1 (The R Foundation for Statistical Computing, <http://www.r-project.org/>).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the derivation cohort and to part of the data in the validation cohorts, and had final responsibility for the decision to submit for publication.

Results

Derivation cohort

The derivation cohort was mainly (91%) of European origin. Baseline characteristics are given in Table 1. At baseline, 7% had CKD stage 3 or 4 and 37% developed ESKD during follow-up. The majority of the ESKD cases were among participants with an $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$ (Supplemental Table S1). This group was characterised by a high degree of micro- or macroalbuminuria (45% vs 19% in the total cohort). Participants were followed for a median of 10.4 years (interquartile limits, 5.1 to 14.7) during which 303 (5.5%) developed

ESKD and 764 (14.0%) died of non-ESKD related causes without having developed ESKD. The incidence rate of ESKD was 5.7 per 1000 person-years.

The final *core model* for cumulative risk of ESKD included age, sex, diabetes duration, eGFR, micro- and macroalbuminuria, systolic blood pressure, HbA_{1c}, smoking and previous CVD. Older age was associated with a lower rate of ESKD but with a higher rate of mortality. For the remaining predictors, more unfavourable levels were associated higher rates of both ESKD and death (Table 2). In the *extended model*, increasing levels of haemoglobin and mild/moderate retinopathy was associated with a higher rate of ESKD but a lower rate of death. Higher levels of UACR was further associated with higher risk of ESKD and death. BMI, triglycerides, regular exercise and sodium was associated with the rate of mortality and thereby indirectly associated with the cumulative risk of ESKD (Supplemental Table S2). Overall, the results of the survival tree analyses were consistent with the difference in baseline characteristics between individuals who do and do not develop ESKD (Supplemental Table S1 and Figures S1-S4).

The estimated impact of calendar time was small (< 2% difference in incidence rate per calendar year) and was not statistically significant ($P \geq 0.241$ for ESKD, $P \geq 0.066$ for death). Hence, calendar time was not included.

The *core model* showed excellent and robust discrimination with C-statistics of 0.872 and above over the 10 years of follow-up in the derivation data. Model calibration was good for up to five years. The *extended model* had slightly better performance with C-statistics of 0.883 and above and good calibration for up to six years (Figure 1 and Supplemental Table S3). Details on the estimated model parameters with- and without post-estimation shrinkage and how to apply them in the cumulative risk model are given in Supplemental Table S4 and S5.

In the sensitivity analysis, including pre-baseline change in eGFR in the *core model* had little effect with an incidence rate ratio below 1% for a 10-unit difference in eGFR change ($P = 0.078$). Also, discrimination for a 5- and 10-year ESKD event was not improved ($P \geq 0.290$) and model calibration was unchanged.

Validation cohorts

The Danish FDDDB cohort of 3,150 adults were followed between January 1st, 2003 to December 31st, 2016 and was representative of the T1D population in that region. They were on average five years older at diabetes diagnosis, macroalbuminuria and severe retinopathy was less frequent and current smoking was around half of that in the derivation cohort (Table 1). Median (IQR) years of follow-up was 10.7 (5.8; 13.6) during which 147 (4.7%) developed ESKD and 422 (13.3%) died from non-ESKD causes, corresponding to an incidence rate of ESKD of 4.9 per 1000 person-years. The *core model* without shrinkage of the parameters performed best. Discrimination was excellent and robust over time with a C-statistic of 0.871 for an ESKD event within 5 years and 0.866 for an event within 10 years. Model calibration was good for up to 5-6 years of follow-up (Figure 1 and Supplemental Table S3). In the subgroup with baseline eGFR ≥ 60 mL/min/1.73m², C-statistic was 0.744 (95%CI: 0.641; 0.847) and 0.775 (0.711; 0.840) for a 5-year and 10-year ESKD event. Model calibration was adequate ($P \geq 0.097$).

The SDRNT1BIO cohort of 6,025 adults were followed between January 1st, 2011 to December 31st, 2018 and was representative of the T1D population in Scotland. The SDRNT1BIO population was slighter older and with around five years longer diabetes duration at baseline. The majority (89%) was of white ethnicity. Like the FDDDB population, they had

less macroalbuminuria and severe retinopathy and the prevalence of current smoking was around half of that in the derivation cohort. The SDRNT1BIO population had almost twice as many using RAS blocking agents and with five times as many using lipid-lowering medications (Table 1). Median (IQR) follow-up was 6.9 (6.2;7.4) years during which 95 (1.6%) developed ESKD and 321 (5.3%) died from non-ESKD causes, corresponding to an incidence rate of ESKD of 2.4 per 1000 person-years (Table 1). The performance of the *core model* was similar with and without shrinkage of the parameters. For the model without shrinkage, discrimination was excellent and robust with a C-statistic of 0.961 for an ESKD event within 5 years and 0.952 for an event within 8 years (the maximum follow-up time). Calibration was only borderline acceptable the first 4-5 years for the *core model* (Figure 1 and Supplemental Table S3).

Discussion

We have derived and validated a high-performing model for predicting individual risk of ESKD in the adult T1D population based on predictors routinely collected in the clinic. An extension of the model to include less frequently measured factors did not substantially improve prediction, suggesting that the more parsimonious *core model*, which is more feasible in a clinical setting, is preferable for assessing individual 5-year ESKD risk in persons with T1D.

The ESKD cumulative incidence rates in the Danish derivation- and validation cohort was twice that of the validation cohort from Scotland and considerable higher than previously reported in Sweden and Finland.^{3,26} The annual incidence rates in the derivation cohort only decreased slightly over the 2001-2016 follow-up period. The referral criteria for persons with T1D are comparable in Denmark and Scotland, and the selection criteria for the cohorts was similar, except that the Scottish cohort did not include persons diagnosed with T1D after age

50. A possible explanation for the difference in ESKD risk could be the more aggressive treatment with RAS blockers and a lower prevalence of smoking in Scotland.

The predictors included in the *core model* have previously been found to be associated with ESKD.^{2-4,15} However, no studies have combined them into a model for predicting individual risk of ESKD in T1D. Only one model for ESKD has been developed in a population representative T2D cohort of mainly white ethnicity.¹¹ When applied to our T1D population, we found discrimination to be adequate for a 5-year ESKD event (C-statistic: 0.790 (0.688; 0.893) but calibration was poor ($P < 0.001$).

Male sex was associated with increased risk of ESKD in our model which is in line with previous studies.^{3,15} A study from New Zealand found male sex to be associated with decreased risk of ESKD, but not when including eGFR in the model.¹¹ The finding in a Swedish study of no risk difference in men and women diagnosed before puberty²⁶ was not supported by the survival tree analysis in our study where no interaction between sex and age and diabetes duration was found.

Although, ESKD is more frequent in old age,^{4,15} the rate of ESKD is decreasing with age in our model. This is likely due to a healthy survivor effect driven by the strong association between age and mortality. In other words, old age may seem protective of ESKD because old people die before they develop ESKD. This finding is in line with another competing risk analysis of ESKD risk in T1D who have macroalbuminuria and CKD stages 1–3.¹⁵

RAS blocking agents and other antihypertensive treatment did not improve the models. Similar result was found in 1000 persons with T1D followed for 25 years in the US where the

association of antihypertensive medication with ESKD was lost when eGFR was included in the model.⁴

Some studies have shown a decline in ESKD incidence over time.^{3,4} However, calendar time was not associated with ESKD in our model, indicating that any observed decline in ESKD over the years is reflected in the change in risk factor levels.²⁷ This is supported by the WESD study from the US where an observed decline in incidence of ESKD over time was explained by improvements in glycaemic- and blood pressure control.⁴

Our *core model* is adequate for assessing 5-year risk of ESKD but predictions beyond this is questionable. Previous models have also primarily been assessed for 5-year risk of ESKD^{11,13} although one model in T2D was well calibrated up to 8 years of follow-up.¹²

Strengths and limitations

We had access to detailed data from repeated clinical examinations for the study participants, which allowed us to update the values of the predictors during follow-up to give a more correct estimate of the associations between the predictors and the event. In addition, missing data was imputed, thereby removing selection bias.

The derivation cohort was mainly of white ethnicity which may explain why ethnicity was not predictive in the models, and further validation in populations of non-White ethnicity is needed.

Our models were developed based on data collected at a single clinical examination. Although, recent studies have found historical measures of eGFR to improve prediction of future eGFR

levels in T1D² and ESKD in the general population,²⁸ pre-baseline change in eGFR in addition to baseline eGFR level did not improve prediction of future ESKD in our study.

In the future, prediction models for ESKD may also benefit from the inclusion of novel biomarkers or with various omics data. However, such biomarkers which are not used or collected routinely in clinical practice have yet to prove predictive beyond that of clinical data.

Clinical perspective

Although age-specific prevalence and incidence of ESKD have been stable since 2006 in Denmark,¹ the actual number of T1D developing ESKD is increasing due to the general ageing of the population. Mortality is still 70% higher in T1D compared with T2D,²⁹ and quality measures of diabetes care in Denmark indicate a less aggressive approach to manage cardiovascular risk factors in T1D.³⁰ Early treatment could prevent or at least postpone the development of ESKD and hereby reduce treatment expenses and increase quality of life in T1D.

Our prediction model was developed for the entire range of eGFR not within the ESKD diagnostic range. Although, persons with CKD stage 3 and 4 are likely already managed as a high-risk group, they will not all develop ESKD. In contrast, the majority of the ESKD events occurs among persons considered at low risk with baseline eGFR ≥ 60 mL/min/1.73m². Our model also performed well in this subpopulation, and we believe ESKD risk assessment is relevant at all levels of eGFR.

Conclusion

We have derived and validated a novel, high-performing ESKD prediction model for risk stratification in the adult T1D population. This model may improve clinical decision making and potentially guide early intervention.

Contributors

D.V., F.P., P.R. and M.E.J. conceived of the study concept and design. D.V. and G.S.A. analysed the data. All authors took part in the interpretation of the results, commented on the manuscript and had final responsibility for the decision to submit for publication. D.V. is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

D.V. and G.S.A. own shares in Novo Nordisk A/S. F.P. reports having received research grants from Astra Zeneca and lecture fees from Astra Zeneca, MSD, Janssen, Eli Lilly, Boehringer Ingelheim, Novo Nordisk A/S, and Novartis, as well as being a consultant/advisory board member for Astra Zeneca, Bayer, Amgen, and MSD. P.R. has served as a consultant for Astra Zeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, Merck, Mundipharma, Vifor, Sanofi, and Novo Nordisk A/S (all honoraria to his institution) and received research grants from Astra Zeneca and Novo Nordisk A/S. M.E.J. has received research grants from AstraZeneca, AMGEN, Sanofi Aventis and Boehringer Ingelheim (investigator-initiated research). M.E.J. also owns shares in Novo Nordisk A/S. A.H. declares no competing interests.

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Data sharing

Due to Danish GDPR rules, the individual level data in this study will not be made available to others. Access to the data sources used in the study must be approved by the Danish Data Protection Agency and the Danish Patient Safety Authority.

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Table 1 Characteristics of the study populations at their first clinical examination in the derivation cohort and for the validation cohorts

	Derivation cohort	Validation cohorts	
	SDCC	FDDB	SDRNT1BIO
N	5460	3150	6025
Follow-up time (years)	10·4 (5·1;14·7)	10·7 (5·8;13·6)	6·9 (6·2;7·4)
Region of origin (%)			
European	91·3	-	-
Middle East	6·1	-	-
Other	2·6	-	-
Age (years)	42·3 (16·5)	42·8 (16·7)	45·1 (15·0)
Males (%)	54·1	57·8	56·1
Age at diabetes diagnosis (years)	21·0 (12·2;33·8)	26·1 (14·3;40·4)	21·6 (12·1;32·2)
Diabetes duration (years)	15·6 (6·6;27·4)	10·9 (2·5;21·9)	20·3 (11·0;30·9)
HbA _{1c} (mmol/mol)	69·4 (16·7)	67·0 (18·8)	71·1 (17·0)
HbA _{1c} (%)	8·5 (1·5)	8·3 (1·7)	8·7 (2·0)
BMI (kg/m ²)	24·7 (3·7)	25·2 (4·3)	27·1 (5·0)
UACR (mg/g)	8·0 (4·0;19·0)	10·6 (4·5;26·8)	8·8 (5·1;25·7)
Albuminuria (%)			
Normal	81·0	76·8	83·1
Micro	13·0	19·9	12·6
Macro	6·0	3·4	4·3
Serum creatinine (μmol/L)	82·0 (69·0;93·0)	-	-
eGFR (mL/min/1·73m ²)	99·8 (84·3;114·6)	89·5 (75·1;104·2)	100·0 (84·3;111·4)
eGFR categories (%)			
eGFR ≥ 90	66·6	49·3	-
60 ≤ eGFR < 90	26·3	41·8	-
30 ≤ eGFR < 60	6·0	8·1	-
15 ≤ eGFR < 30	1·1	0·8	-

Haemoglobin (mmol/L)	8.7 (0.8)	-	-
Potassium (mmol/L)	4.0 (0.4)	-	-
Sodium (mmol/L)	138.8 (3.0)	-	-
TSH ($\times 10^{-3}$ IU/L)	1.5 (0.9;2.2)	-	-
Systolic blood pressure (mmHg)	132.1 (19.2)	130.9 (18.3)	130.8 (16.0)
Diastolic blood pressure (mmHg)	78.0 (10.0)	77.7 (10.5)	75.4 (10.0)
Total cholesterol (mmol/L)	4.9 (1.0)	4.9 (1.0)	-
HDL cholesterol (mmol/L)	1.6 (0.5)	1.7 (0.5)	1.5 (0.5)
LDL cholesterol (mmol/L)	2.7 (0.9)	2.7 (0.9)	2.5 (1.0)
Triglycerides (mmol/L)	1.0 (0.7;1.5)	1.0 (0.7;1.5)	1.1 (0.8;1.7)
RAS blockers (%)	21.6	8.9	37.3
Other antihypertensive treatment (%)	26.9	7.1	28.1
Lipid-lowering medication (%)	10.4	9.3	52.1
Retinopathy status (%)			
No apparent retinopathy	46.3	50.1	38.5
Mild/moderate	22.0	32.5	34.9
Severe	31.7	17.5	26.6
Current smoking (%)	51.3	27.1	21.9
Alcohol intake (%) [#]			
0 units/week	14.5	-	15.2
1-20 units/week	80.6	-	71.9
> 20 units/week	4.8	-	12.8
Regular exercise (%) [†]	69.1	56.7	40.0
Previous CVD (%)	8.9	9.4	6.8

Data are means (SD), medians (interquartile limits), or percentages.

BMI: body mass index; eGFR: estimated glomerular filtration rate calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration standard equation.; HbA_{1c}: haemoglobin A1c; UACR: urinary albumin-to-creatinine ratio; TSH: thyroid-stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CVD: Cardiovascular disease; ESKD: end-stage kidney disease.

[#]A unit alcohol: 12 g of pure alcohol. [†]Regular exercise: ≥ 30 minutes per day

Table 2 Incidence Rate Ratios (IRR) for predictors of ESKD and death and postestimation shrinkage factors - *core model*

	ESKD		Non-ESKD death	
	IRR (95%CI)	P value	IRR (95%CI)	P value
Age (10 years)	0.83 (0.75;0.92)	<0.001	-	
Male sex (vs female sex)	1.40 (1.11;1.78)	0.005	5.47 (2.58;11.61)	<0.001
Diabetes duration (10 years)	1.13 (1.02;1.25)	0.022	1.11 (1.05;1.16)	<0.001
eGFR (halving)	8.15 (6.88;9.65)	<0.001	1.28 (1.11;1.49)	<0.001
Microalbuminuria (vs normoalbuminuria)	1.09 (0.76;1.55)	0.643	1.64 (1.39;1.94)	<0.001
Macroalbuminuria (vs normoalbuminuria)	1.89 (1.32;2.70)	<0.001	2.39 (1.88;3.02)	<0.001
Systolic blood pressure (10 mmHg)	1.08 (1.03;1.14)	0.004	0.90 (0.86;0.93)	<0.001
HbA _{1c} (10 mmol/mol)	1.12 (1.03;1.20)	0.005	1.10 (1.04;1.15)	<0.001
Smoking (vs no smoking)	1.27 (1.00;1.62)	0.048	1.88 (1.63;2.18)	<0.001
Previous CVD event (vs no)	1.35 (1.05;1.74)	0.019	1.93 (1.65;2.25)	<0.001
Age (10 years), women	-		2.37 (2.18;2.59)	<0.001
Age (10 years), men	-		1.92 (1.78;2.07)	<0.001

ESKD: end-stage kidney disease; CVD: Cardiovascular disease;

IRR (95%CI): incidence rate ratios with 95% confidence intervals

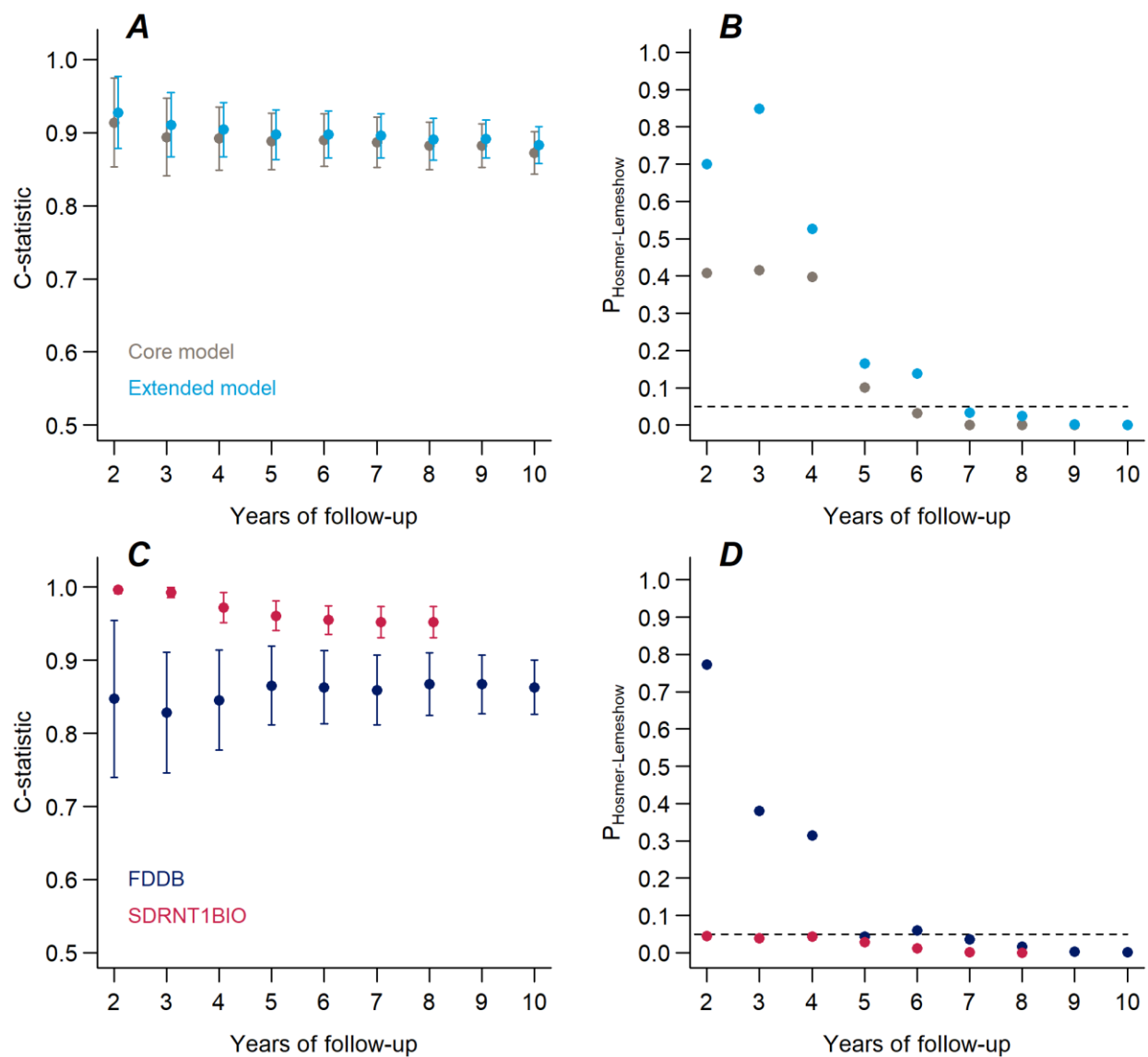


Figure 1 C-statistic for an end-stage kidney disease event within years of follow-up time in the derivation cohort (A) and in the validation cohorts (C), and p-value for test of adequate model fit in the derivation cohort (B) and in the validation cohorts (D). The dotted horizontal lines in (B) and (C) denotes the threshold for acceptable model calibration (acceptable above the dotted line). FDDB: the Funen Diabetes Database. SDRNT1BIO: the Scottish Diabetes Research Network Type 1 Bioresource



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Necessary Additional Data

Predicting end-stage kidney disease in type 1
diabetes_add.pdf

